BIOLOGICAL RHYTHMS AND SHIFT WORK

BIOLOGICAL RHYTHMS AND HUMAN PERFORMANCE

Scott S. Campbell

Institute for Circadian Physiology
Boston, Massachusetts

This contractor document was prepared for the OTA report entitled *Biological Rhythms and Shift Work*. It is being made available because it contains much useful information beyond that used in the OTA report. However, it is not endorsed by OTA, nor has it been reviewed by the Technology Assessment Board. References to it should cite the contractor, not OTA, as the author.

Submitted: July 21, 1989

J952-77

BIOLOGICAL RHYHTMS AND HUMAN PERFORMANCE

INTRODUCTION

Definitions and Focus

Biological rhythms comprise those events within a biological system that recur at more-or-less regular intervals (Kalmus, 1935; Aschoff, 1981). A common way to classify such rhythms is by the frequency of their recurrence and this can range from several cycles per second to one cycle per several years. Not surprisingly, the most predominant biological rhythms are those which occur in coincidence with the geophysical cycle of day and night -- the *circadian* rhythms.

In response to the natural alternation in light and darkness, virtually all species have developed endogenously mediated rhythms with frequencies close to twenty-four hours. The pervasive nature of such rhythmic components in physiology and behavior suggests that this circadian (circa = about, dies = day; Halberg, 1959) temporal organization is vital to the overall well-being of the organism. Among the numerous systems and functions mediated by the circadian timing system are hormonal output, body core temperature, rest and activity, sleep and wakefulness, and motor and cognitive performance. In all, literally hundreds of circadian rhythms in mammalian species have been identified (see for example, Aschoff, 1981; Conroy & Mills, 1970), and Aschoff (1965) has noted that "there is

apparently no organ and no function in the body which does not exhibit a similar daily rhythmicity".

Because of the predominance of rhythms recurring about once a day, biological rhythms with longer or shorter frequencies have typically been classified as *infra*dian, or *ultra*dian rhythms, respectively. An example of an infradian rhythm is the human menstral cycle. An example of an ultradian rhythm is the recurrence of dream sleep (REM sleep) about every 90 minutes throughout a normal night's sleep.

It is rhythms in the circadian range, and to a lesser extent the ultradian range, that are of primary relevance to the topic of this paper. Most performance measures show oscillations in the 24-hour range, though considerable evidence suggests shorter-term fluctuations, as well. Likewise, the human sleep/wake cycle, which so profoundly influences performance, is primarily a circadian system, but with important ultradian components.

Discovery of Circadian Principles

Because of their close link to the solar day, it was long believed that circadian rhythms were actually the product of such environmental cues. The proof that biological rhythms are regulated, instead, by factors inherent to the organism, could be derived only from studies of organisms living in the absence of external factors which may provide cues to time of day or, more generally, to the passage of time. The first published study to utilize such a methodology reported on the daily leaf movements in a plant, Mimosa

pudica (de Mairan, 1729; cited by Bunning 1960). Though the plant was kept in total darkness, its leaves continued to exhibit closure and unfolding at times roughly corresponding to dusk and dawn. The further discovery, a century later, that such leaf movements showed a periodicity close to, but distinctly different from, the natural 24-hour cycle of light and darkness (de Candolle, 1832) provided perhaps the clearest indication that such rhythms were driven by endogenous mechanisms, rather than being the product of environmental stimuli. In the following decades, thousands of investigations established the existence of similar "free-running" rhythms in species ranging from single-celled organisms to a wide variety of laboratory species. However, another 130 years were to pass before the first attempts were made to study temporal components of human physiology and behavior under analogous experimental conditions.

Human Circadian Rhythms. -- In the early 1960's, Aschoff and co-workers initiated a series of studies which, over the next 20 years, would lay the groundwork for much of what is known today about the human circadian system (for a comprehensive summary of much of this work, see Aschoff & Wever, 1981; Wever, 1979). All but a few pilot studies were conducted in an underground laboratory consisting of two studio apartments which were free of all environmental cues to time of day. The laboratory was heavily sound-dampened and the timing and intensity of illumination could be controlled from outside the apartments by the experimenters. In addition,

subjects were studied in isolation in order to eliminate possible time cues provided by social contact.

The first experiments conducted in this unique environment (Aschoff & Wever, 1962; Aschoff, 1965) established that adult humans exhibit "free-running" rhythms of rest and activity averaging slightly longer than 25 hours (Figure 1). That is, a subject's average "day" continued for about an hour longer than the natural day, though in some people the subjective day continued for a substantially longer period (up to 50 hours). Thus, subjects who thought that they had been in the time-free environment for, say, three weeks were often quite surprised when they were informed that a month or more actually had elapsed!

Further investigations of numerous other systems confirmed that in humans, endogenous daily rhythms tended to "free-run" at frequencies slightly longer than 24 hours, and that all such rhythms typically stayed synchronized with one another (for a complete review, see Moore-Ede, et al., 1982). This internal organization among rhythms is seen clearly in the usual relationship between the sleep/wake system and the rhythm of body temperature. In the time-free environment, major sleep episodes tend to be initiated around the low point (nadir) of the temperature rhythm and are terminated several hours after the nadir (see Figure 1). Aschoff and Wever observed remarkable interindividual precision in the period length of the sleep/wake

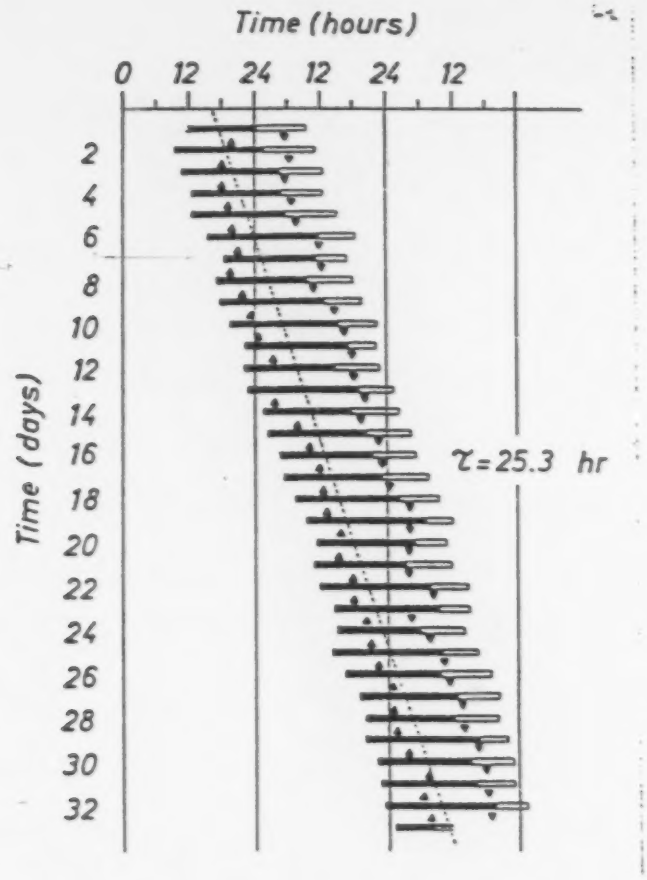

Figure 1. Free-running rhythm of a subject living in an environment without time cues. Rest (white bars) and activity (black bars) are presented as a function of time of day for successive subjective days of the study. The daily maximum (▲) and minimum (▼) of body core temperature are also shown. Note the consistent relationship between the temperature minimum and the onset of the rest period. (From Wever, 1979).

rhythm under these conditions. The average 25-hour rhythms deviated only about one half-hour between individuals (Wever 1979).

For any single individual, however, the day-to-day flexibility of the circadian system is both obvious and well-documented (Webb & Agnew, 1978). We are not suddenly overcome with sleep at a particular point in our temperature rhythm, nor are we startled awake each morning by a biological alarm clock tied to the temperature cycle. Rather, we routinely shift our bedtimes and wakeup times to accomodate changes in our daily schedules. At the level of individual behavior, then, the human circadian system is a "sloppy" system (Campbell, 1984; Campbell & Zulley, 1988). It is this inherent flexibility in the system that allows our "free-running" endogenous rhythms to be synchronized, or *entrained*, by the numerous environmental, behavioral and social cues that provide the structure of our daily lives.

Does such sloppiness in human biological rhythms imply the existence of a "sloppy" clock to control them? The identification and nature of the brain mechanisms involved in the regulation of circadian rhythms, the "biological clocks", are the topic of the next section.

BIOLOGICAL BASIS OF CIRCADIAN RHYTHMS

Neural Substrates

At about the time that Aschoff and others were conducting their behavioral studies of human circadian rhythms, Richter (1965) was

completing a series of experiments in rats, designed to localize the brain areas responsible for circadian rhythms generation. Of the endocrine systems and literally hundreds of various brain areas that he experimentally destroyed, only lesions placed in the hypothalamus (see Figure 2) caused alterations in the animals' free-running circadian rhythms (Richter, 1967). Further experiments led to the identification of a more descrete area within the hypothalamus where ablation caused the total loss of circadian rhythms of feeding, drinking and activity.

The specific cells involved were subsequently identified by researchers conducting studies to identify neural connections between the visual system and the brain (Moore & Lenn, 1972). Based on the knowledge that the daily light/dark cycle is a primary synchronizer of circadian rhythms, Moore and co-workers reasoned that certain retinal projections should terminate in brain areas that control the rhythms. One such projection terminated in the *suprachiasmatic nuclei (SCN)* and, indeed, when these cells were destroyed in laboratory rats, circadian rhythmicity was completely eliminated (Moore & Eichler, 1972; Stephan & Zucker, 1972). Many additional experiments, using numerous techniques (e.g., Inouye & Kawamura, 1979; Lehman, et al., 1987; Rusak & Groos, 1982) established in the minds of most scientists that the SCN function as an endogenously generated circadian pacemaker -- a biological clock.

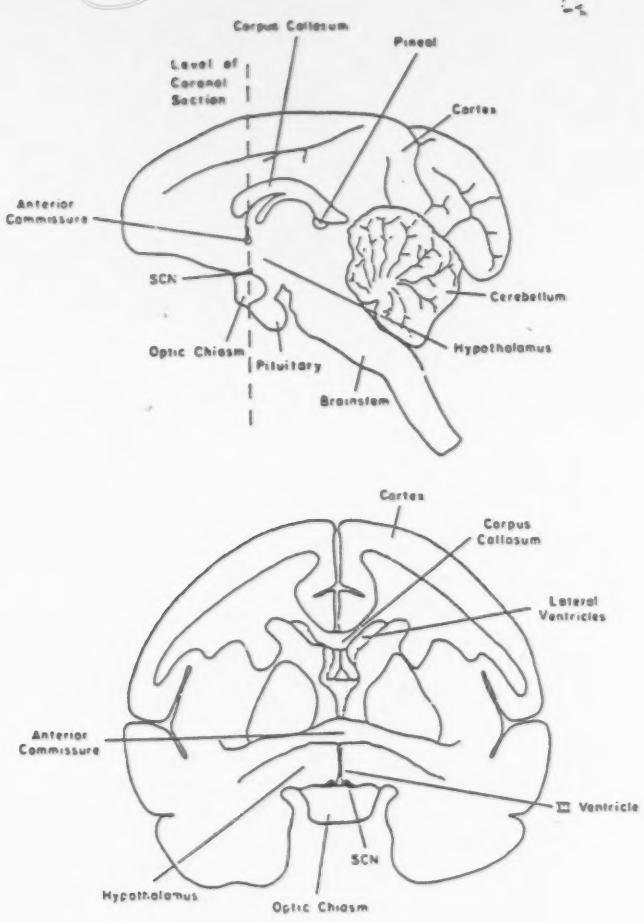

Figure 2. Schematic diagram of the brain of the squirrel monkey: a midline sagittal view (top) and a front view at the plane of the optic chiasm (below). The suprachiasmatic nuclei (SCN) are situated in the hypothalamus directly above the optic chiasm. The SCN are strongly influenced by the environmental light/dark cycle via the retinohypothalamic tract and may be influenced by melatonin secretion from the pineal gland (see page 10). (From Moore-Ede, et al., 1982).

Although it seems certain that the SCN are the locus of a dominant circadian clock, the exact nature and role of the clock remains unclear. A number of studies (e.g., Fuller, et al., 1981; Prosser & Satinoff, 1984; Terman & Terman, 1985) have shown that some rhythms actually do persist, often in the ultradian range, following SCN ablation. These findings suggest that there are other brain areas that may also have the capacity to function as independent oscillators. For example, rhythmic components of feeding behavior appear to be mediated by areas of the hypothalamus separate from the SCN (Mistleberger & Rechtschaffen, 1984; Mistleberger & Rusak, 1989). Similarly, the failure of SCN ablation to affect circadian rhymicity in visual sensitivity to light in rats (Terman & Terman, 1985) suggests the existence in mammalian species of a retinal pacemaker (Mistleberger & Rusak, 1989). It has been proposed, as well, that even the SCN may comprise not one, but two or more primary oscillators that are typically joined, but which may become functionally dissociated under certain conditions.

While a great deal more research is required in order to clarify the structure and function of the neural mechanisms regulating biological rhythms, the concept of a hierarchy of circadian oscillators, dispersed throughout the brain and possibly other organs (for reviews, see Mistlberger & Rusak, 1989; Moore-Ede, et al., 1982), appears to be justified. At least one, and quite possibly several, dominant pacemakers act to synchronize a number of subordinate oscillatory systems to a common frequency. In the

absence of influence from the dominant pacemaker(s), the underlying periodicities of subordinate oscillators may become apparent.

Further research is also required in order to clarify the role of neuroendocrine systems in circadian regulation, though there is a growing body of evidence that various hormones may have a regulatory influence on the timing of circadian rhythms (Mistleberger & Rusak, 1989). Perhaps the most important of these is the system governed by the pineal gland which serves as the primary locus of melatonin production (for a review, see Reiter, 1988, 1989). Although the role of melatonin in regulating seasonal reproductive cycles in a number of species has been established, its function in humans remains unclear. Melatonin production is cyclic and is sychronized to the 24-hour environmental light/dark cycle. The recent finding of putative melatonin receptors in the SCN of humans (Reppert, et al., 1988) suggests that melatonin may be instrumental in the modulation of entrainment by the light/dark cycle of human circadian rhythms.

Timing of the Circadian System

It was pointed out in the previous section that the human circadian timing system is characterized by a certain degree of lability, or "sloppiness", at least with respect to behavioral expressions of the system (e.g., the timing of sleep and wakefulness). This is, by no means, a consistent finding across the animal kingdom, however. Rather, the degree of precision with which the timing of circadian rhythms is expressed varies widely across species

(Moore-Ede, et al., 1982). For example, as shown in Figure 3., the mouse exhibits a highly precise circadian rhythm in wheel-running, whereas, the circadian component of rest\activity in the domestic cat is virtually absent. In addition to differences in precision, there are also species-related variations in free-running period length. A discussion of the complex interactions between species, environmental conditions, physiological state and other variables that determine period length (Aschoff, 1978) is beyond the scope of this report. However, such differences, as well as those associated with the precision of the timing system, must be considered carefully when making inferences based on animal studies about the nature of human circadian rhythms.

As mentioned earlier, the inherent periodicity of even the most dominant and precise pacemaker becomes apparent only under conditions in which external time cues are completely eliminated, allowing the biological clock to "free-run". This is clearly an artificial situation that occurs only under the most stringent laboratory conditions. When circadian rhythms are observed in daily life, out in the real world, they reflect not only the control imposed by a hierarchy of internal pacemakers. They also reveal the powerful influence imposed on the system by factors external to the organism.

Zeitgebers and Entrainment. -- The term Zeitgeber (literally, *time giver*, in German) was coined by Aschoff (1951) to designate the constellation of external influences that synchronize, or *entrain*, the endogenous circadian

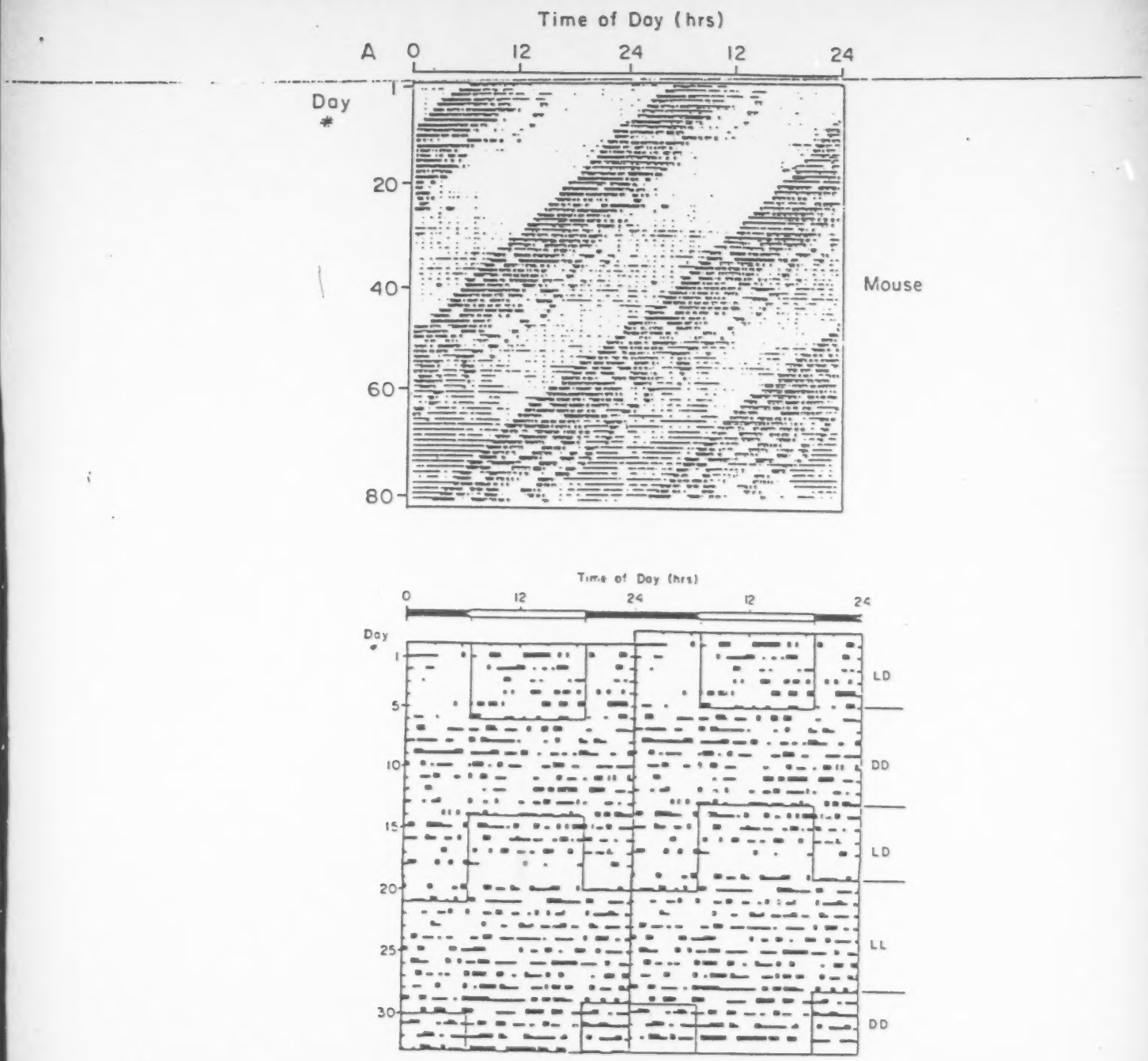

Figure 3. A comparison of the free-running rest/activity patterns of a mouse (top) and a domestic cat (below). Note the regularity with which activity is initiated by the rodent. Also note the period length of the mouse's free-running circadian rhythm. In contrast to the human profile shown in Figure 1, the mouse exhibits a periodicity of *shorter* than 24 hours.

system to an exact frequency. Other terms, synonomous with zeitgeber, include "time cue", "synchronizer", "entrainer" and "entraining agent". Without question, the geophysical cycle of day and night provides the strongest zeitgeber for virtually all organisms. However other factors, such as ambient temperature, food availability and particularly in humans, social cues, have also been demonstrated to effectively entrain endogenous rhythms.

Entrainment does not occur abruptly following the introduction of a zeitgeber. Rather, the circadian system adjusts to new entrainment schedules gradually, with the various overt rhythms (e.g., sleep/wakefulness, body temperature, performance efficiency) requiring different lengths of time to become fully synchronized to the new time cues. A dramatic, yet commonly experienced, example of this process of *re-entrainment* is jet lag. Figure 4 illustrates the differential re-entrainment times required by a number of circadian measures following east- and west-bound flights over six time zones. Only after about eight days do the rhythms become re-synchronized to one another and entrained to the new zeitgebers (primarily, local time and social cues).

The sleep/wake system, though not one of the measures shown in the figure, is also significantly affected by the shift to newly-timed zeigebers. Since the daily timing of the sleep/wake rhythm is in large part a behavior dictated by social constraints, bedtimes and rising times are often immediately entrained to the new Zeitgeber. That is, we choose to time our sleep in the

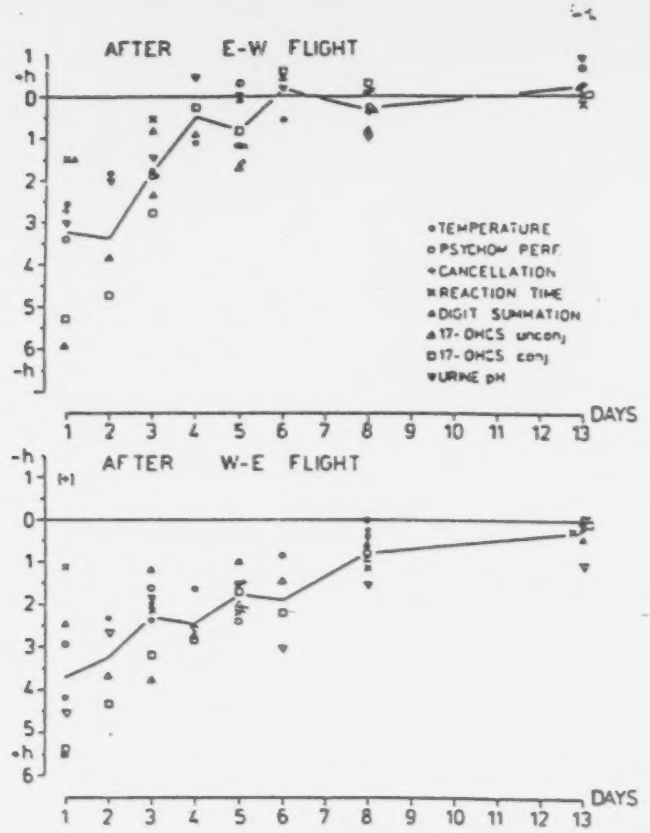

Figure 4. Time required for re-entrainment of various circadian parameters following west-bound (top) and east-bound (below) flights over 6 time zones. Solid lines represent mean values of the acrophases obtained from the different measures (individual symbols). Re-synchronization of parameters does not occur until at least Day 8. (From Wegman & Klein, 1985).

new environment to coincide with local time. However, both subjective reports and objective electroencephalographic (EEG) findings indicate that actual sleep time is reduced and sleep quality is drastically compromised during the re-entrainment process (Akerstedt, 1985; Dement, et al., 1986; Graeber, et al., 1986; Sasaki, et al., 1986; Wegman, et al., 1986). As with the other circadian variables discussed, more than a week may be required for sleep to become fully entrained to a shift in the timing of zeigebers (Athanassenas & Wolters, 1978; for a review, see Winget et.al., 1984).

As will be discussed in the next sections, this property of the circadian system to only gradually entrain to a change in the timing of zeitgebers is at the root of many problems associated with shift work and performance.

BIOLOGICAL RHYTHMS OF HUMAN PERFORMANCE

Following the initial discovery of rhythmicity in numerous physiological systems, it was soon ascertained that many human psychological processes and mental functions exhibited fluctuations across the day, as well. These included subjective assessments of alertness and mood and objectively measured efficiency in a wide range of performance tasks. And, just as the sleep/wake system was found to be synchronized to the circadian rhythm of body temperature, human performance efficiency was also found to show a tendency to parallel the rise and fall of the temperature rhythm. This relationship is illustrated in Figures 5 a and b. (It should be emphasized

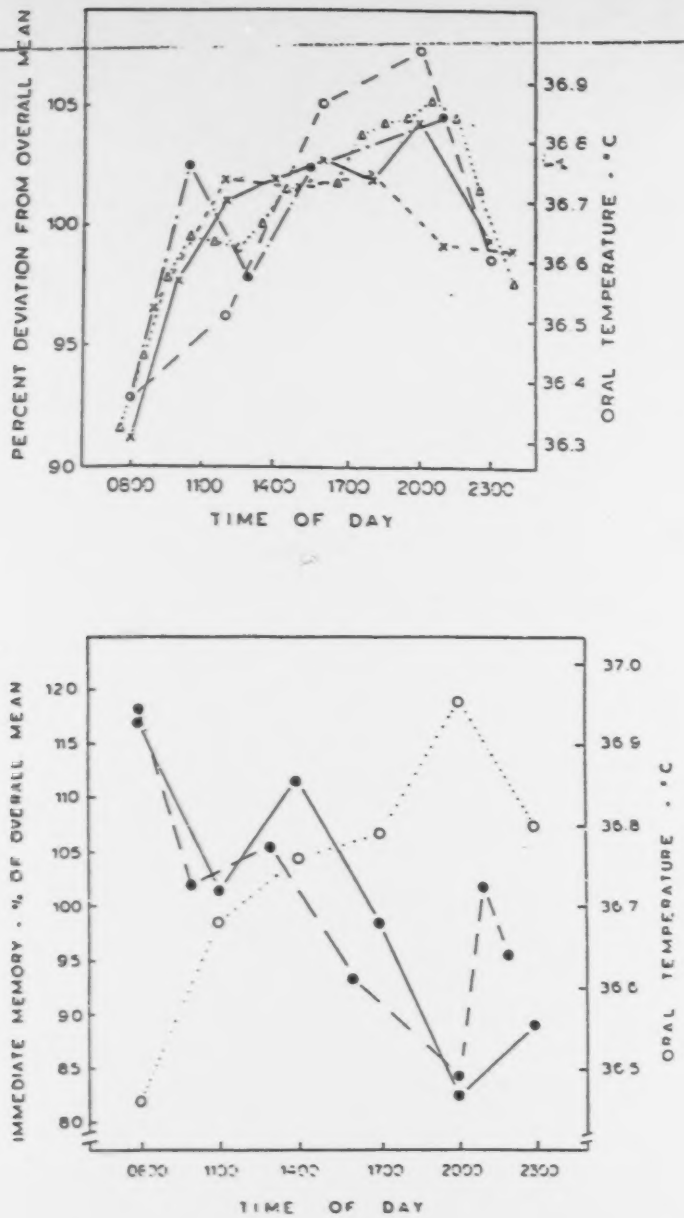

Figure 5. Illustration of the relationship between the circadian rhythm in body temperature (here, oral temperature) and efficiency on various performance tasks. The top graph shows the general tendency for performance efficiency to parallel the course of temperature. The bottom panel shows an opposite relationship, however, between oral temperature and tasks involving short-term memory (see pages 18 and 19). (From Folkard and Monk, 1985).

here that no causal relationship is implied, nor should one be inferred, when the temporal link between temperature and rhythms of performance or sleep/wakefulness is considered. Rather, body temperature is a convenient and traditional "marker" of the endogenous circadian clock against which to reference other variables showing systematic changes as a function of time of day, particularly "psychological" measures such as performance efficiency and mood (Monk, 1989)).

Methodological Considerations. -- Several difficulties inherent in the study of rhythmic aspects of performance must be considered prior to a discussion of the findings (for a full discussion of these points, see Colquhoun, 1981; Folkhard & Monk, 1985). First, and perhaps most important, performance tasks are performed voluntarily. As such, unlike physiological processes, performance efficiency may be dictated in part, or wholly, by motivation of the subject. The question must be asked, then, is an observed "rhythm" in task performance an actual reflection of time-of-day changes in cognitive efficiency, or simply a reflection of fluctuations in motivation to perform? On the other hand, if a periodicity in performance is not observed, does this mean a rhythm does not exist, or simply that changes in motivation across the day have effectively masked, or "washed out", the underlying rhythm? These often become critical issues when attempting to apply the results of laboratory studies to the workplace, since motivational components of the two setting may differ significantly.

It is also important to keep in mind the obvious fact that performance is a waking behavior. Performance efficiency cannot be assessed when the subject is asleep. Thus, the approximately eight-hour interval of the 24-hour day usually spent in sleep must be filled either by waking subjects periodically throughout the sleep period to do performance tasks, or by extending the usual waking period. Both procedures (sleep interruption and sleep deprivation) are likely to influence the results one obtains. Because of such limitations, Colquhoun (1981) has emphasized that, with respect to the evaluation of temporal components of performance efficiency, the focus is more specifically on "time-of-(waking)-day effects". One method to overcome this problem is to study subjects, for extended periods, in time free environments. As a consequence of their "free-running" sleep/wake cycles, subjects are, at one time or another during the study, awake at all phases of the day. Therefore, given a long enough study, one could obtain "waking day" effects throughout the circadian cycle. To date, however, the data base from such studies specifically addressing performance issues is meager. With these caveats in mind, let us briefly examine the data.

Early studies confirmed that in very general terms, performance measures show gradually increasing levels of efficiency in association with the rising portion of the body core temperature cycle. Under the entrained conditions of daily life, as shown in Figure 5 (top), this corresponds to the interval beginning at roughly 7AM and ending with a peak in performance

in the early evening. The trough in such measures of performance was reported to occur in the very early hours of the morning (approx. 2 to 6 AM), in asssociation with the minimum portion of the body temperature cycle (for reviews, see Colquhoun, 1972; Kleitman, 1963).

Subsequent and inevitably more refined experiments led to the identification of several important qualifications to the general finding of "performance paralleling temperature". First, the nature of the task to be performed was found to be of considerable importance. Many of the procedures employed in the early studies consisted of relatively boring vigilance tasks, requiring little in the way of higher-level cognitive functioning or mental processing. As a greater range of cognitive skills was tested by a larger variety of performance tasks it became apparent that factors such as perceptual involvement, memory load and type (short or long term) and amount of logical reasoning required all were important in determining the exact course of performance efficiency across the day (see, for example, Folkard, et al., 1976).

Moreover, the nature of the measure chosen in evaluating the results was found to have a significant impact on the time-of-day effects observed. For example, Monk and Leng (1982) found that if performance efficiency on a search task was evaluated in terms of speed of response, the usual relationship with temperature was observed -- subjects became faster across

the day. However, if accuracy of response, rather than speed, was the critical measure, then an opposite relationship was observed.

To suumarize, the various qualifications and caveats notwithstanding, there is considerable evidence to indicate that performance efficiency and other psychological processes such as arousal and mood are subject to significant circadian fluctuations. While many performance tasks are closely tied to the rise in body core temperature across the daytime hours, there are clearly measures that deviate from such a relationship. Indeed, in certain cases (e.g., those involving short term memory processes), the relationship between daytime temperature and performance efficiency is an inverse one (see Figure 5, bottom) (Folkard & Monk, 1980; Laird, 1925). However, regardless of the course across the daytime hours, the evidence is overwhelming that performance efficiency declines to minimum levels during the nighttime hours (i.e., the time associated with the trough of body temperature).

Ultradian Components. -- From the very beginning of research on time-of-day variations in performance, a transient decline in task efficiency during the afternoon has been noted (Bechterew, 1893; Kraepelin, 1893). This so-called "post-lunch dip" continues to be the most commonly observed and well-established rhythmic components in the ultradian range (Blake, 1967; 1971; Colquhoun, 1971; Hildebrandt, et al., 1974). Debate continues with respect to the extent of the relationship between meal timing and the

transient drop in performance. Results of an unpublished study by Blake (reported by Colquhoun, 1972) suggest that the afternoon "dip" occurs regardless of meal timing. On the other hand, transient changes in blood glucose levels, pulse rate and body core temperature associated with mid-day meals have also been implicated in the post-lunch declines (e.g., Christie & McBrearty, 1979). There is also evidence to suggest that the post-lunch effect may be closely tied to a biologically-based decrease in alertness (a "nap phase") that occurs, on average, just prior to the maximum of body core temperture (Campbell & Zulley, 1985; 1988; Zulley & Campbell, 1985). In the entrained conditions of daily life, this time of enhanced sleep tendency corresponds roughly to 2 to 4PM, a time when the mid-day dip in performance is commonly observed.

More frequent ultradian fluctuations, in the 90 minute range, have also been observed in brain activity, eye movements, daydreaming, subjective arousal, and ability to go to sleep (Gertz & Lavie, 1983; Kripke, 1972; Kripke and Sonnenschein, 1978; Lavie, 1979; Lavie & Scherson, 1981; Okawa, et al., 1984). These findings support the existence of what Kleitman (1963) termed the Basic Rest-Activity Cycle (BRAC), a 90-minute oscillation in arousal that is manifest not only during waking but also during sleep, in the form of the REM-NREM cycle. While such fluctuations in mental function may potentially influence performance efficiency, results of studies addressing this area are inconclusive (for a review, see Lavie, 1985).

BIOLOGICAL RHYTHMS AND SHIFTWORK

The example of jet lag was used earlier to describe the process of entrainment to new zeitgebers. Consider the situation of having a job in which every week or so, you must move from your office in Los Angeles to your office in London to your office in Tokyo to your office in Los Angeles and so on. While the variety is potentially exciting, you would likely be unable to enjoy it due to your constant state of jet lag.

This is similar to the dilemma of many rotating shift workers. Most rotate work shifts at a rate that does not permit them to benefit from complete entrainment to the new schedule. Instead, they are in a constant state of adjustment. Moreover, they do not have the advantage of social cues to aide the entrainment process. To the contrary, most rotating shiftworkers find themselves fighting the tide of social cues in their efforts to deal effectively with their changing schedules (Folkard, et al., 1985). As such, the adjustment of circadian rhythms to rotating shift work may require even more time than is required in the case of jet lag (for a review of circadian adaptation to shift work, see Akerstedt, 1985). The battle is most severe on the night shift when cultural factors and circadian influences combine to make both on-shift performance and off-shift sleep difficult to manage effectively (Akerstedt, 1984; Akerstedt & Gillberg, 1981).

Investigators have used laboratory studies and, to a lesser extent, real task measures to assess the contribution of biological rhythms to shiftwork issues. Results of such studies are discussed below.

Field Studies. -- Observing workers performing real tasks during round-the-clock operations is perhaps the most logical means of studying circadian influences on shift work. Unfortunately, the difficulties involved in undertaking field studies, particularly access to the working environment, have made such studies rare. Results of six of the most cited real task studies are presented in Figure 6. Whether the measure has been actual task performance (i.e., speed or accuracy of task completion) (Bjerner & Swensson, 1953; Browne, 1949; Wojtczak-Jaroszowa & Pawlowska-Skyba, 1967), or the results of reductions in vigilance (Folkard, et al., 1978; Hildebrandt, et al., 1974; Prokop & Prokop, 1955), the consistent finding has been of significantly reduced efficiency during the nighttime hours. Further inspection of Figure 5, however, reveals that a post-lunch dip was evident in four of the studies; in two of them, the declines were equal in severity to the nighttime dips.

In their discussion of these studies, Folkard & Monk (1985) are careful to point out that the results are probably not entirely attributable to circadian factors. Many other factors that differ as a function of time of day, such as lighting conditions, task type and load, individual motivation, group morale and supervisory demand, can all have an impact on performance.

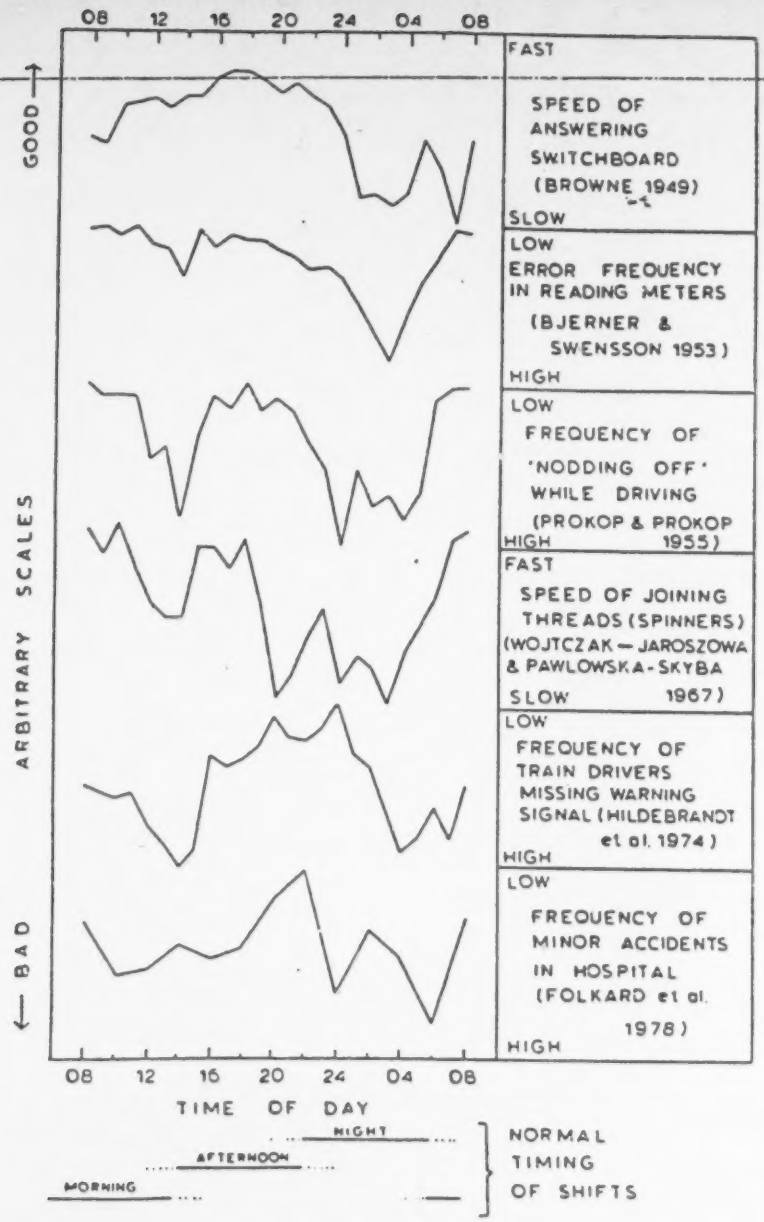

Figure 6. Variations in "real task" measures as a function of time of day. Note the decline in the early morning in all measures, as well as the substantial effects of the "post-lunch dip" in four of the studies. (From Folkard and Monk, 1985).

Nevertheless, there is little question that circadian physiology is an important variable in round-the-clock operations.

Laboratory Studies. In many ways, simulated shiftwork studies are better suited to understanding this circadian contribution. Studies of simulated shift work in the laboratory are undoubtedly easier to accomplish than field research. In addition, the data obtained from lab studies are typically "cleaner" and more extensive. For example, the timing and frequency of task performance can be more stringently controlled and measures such as body temperture and subjective alertness and mood are more readily obtained. However, these advantages do not come without cost. The extent to which findings from laboratory studies can be applied back to real-world settings is limited. Subjects used in laboratory studies seldom have shift work histories and they tend to be younger than the average shift worker. Furthermore, the simulated workplace rarely mimics actual conditions accurately.

Because both physiological and performance variables can be evaluated over extended intervals, a primary focus of simulated shiftwork studies has been the time required for circadian adjustment to take place following a shift change (e.g., from morning to night shift). Colquhoun and co-workers (1968) concluded that the circadian rhythm in body temperature had not completely adjusted following 12 consecutive night shifts. Subsequent studies found that even three weeks on night shift was insufficient for complete circadian adjustment (Knauth, et al., 1978; Weitzman & Kripke, 1981). This

held not only for physiological measures such as temperature and urine volume, but also for mental function and psychomotor tasks (Hughes & Folkard, 1976; Monk, et al., 1978). As with jet lag, the various measures adjusted to the new schedule at differing rates.

There is little indication that the direction of rotation (clockwise -- day-to-evening-to-night shifts versus counter-clockwise -- day-to-night-to-evening) is an important factor in the degree and speed with which circadian rhythms adjust to the change in shifts. Although it has been argued that circadian principles favor a clockwise rotation (Czeisler, et al., 1982), no study has adequately addressed this issue (Turek, 1986).

Of course, the end result of inadequate adjustment is to the night shift is reduced performance efficiency on the job and shorter, less restful sleep at home. Thus, whether the research arena is the laboratory or the workplace, whether the measure of interest is circadian physiology or task efficiency, the findings are consistent. Rotating shift work, particularly the night shift, presents significant problems for human performance. In the last section of this paper, some possible strategies for dealing with these problems will be discussed.

Strategies for Managing Shift Worker Rhythms Disturbance

Shift Scheduling. -- Undeniably, the most effective approach to alleviating the performance deficits that result from inadequate circadian adjustment is to make fundamental changes in shift scheduling. It has been pointed out

that weekly rotations, far and away the most common schedules in American industry, are the most pernicious of all possible schift schedules (Czeisler, et al., 1982). Implementation of permanent (i.e., non-rotating) shift schedules would go far to ease the problems inherent in constant rotation. At the very least, this approach would reduce the proportion of workers affected by having to work the night shift. Even those on permanent night shift may eventually adjust to this reverse cycle, although family and social constraints (e.g., reversion to the "real world" schedule on weekends and days off) may continue to make such adjustment difficult, if not impossible.

Behavioral Interventions. -- In the absence of major changes in shift scheduling procedures, a couple of behavioral interventions seem worth considering. One important consideration in this regard is shift worker awareness and education. A better understanding of the bases of the sleep, performance and circadian rhythms disturbances that they experience daily is likely to make shift workers more willing to accept, and comply with, the various interventions.

There is little question that sleep loss and the resulting on-the-job sleepiness constitute the biggest problem for shift workers (Akerstedt, 1988; Colligan & Tepas, 1986). *Napping strategies* may be useful in addressing this problem in two ways. Brief naps taken during a work shift may enhance subsequent performance, whereas naps taken off shift may help to offset the sleep loss typically associated with shift work schedule.

With respect to on-duty napping, a number of investigators have reported significant improvements in performance efficiency following naps of as little as 20 minutes duration (Stampi, 1989). However, it is clear from these studies that enhanced performance occurs only after the residual effects of sleep have worn off. Such "sleep inertia" can result in performance decrements for up to an hour following intial awakening. Therfore, if on-shift napping is to be considered, it is essential that sleep inertia effects be taken into consideration.

Napping at appropriate times during off-duty hours may also enhance performance by offsetting the sleep loss that typically accompanies rotating shift work. Recent findings confirm that napping is, infact, an integral component of the circadian sleep/wake system (Campbell, 1984; Campbell & Zulley, 1985; 1988; Dinges, 1989). Workers who cannot sleep for longer than 4 to 5 hours during their initial sleep attempt (a common complaint among shift workers trying to sleep during the day) (Foret & Lantin, 1972; Walsh, et al., 1981) may be able to obtain a couple of additional hours if sleep is attempted again at the appropriate "nap phase".

Bright light strategies that were originally developed for treatment of seasonal affective disorders (Lewy, et al., 1982; Rosenthal, et al., 1985) may also provide benefits for shift workers. The circadian phase-shifting and entraining properties of timed exposure to bright light are now well-documented (Czeisler, et al., 1986; Eastman, 1986, 1987; Lewy, 1987; Wever,

et al., 1983). Also documented is the fact that healthy young adults receive remarkably little exposure to environmental bright light (Savides, et al., 1986) and that exposure declines with age (Campbell, et al., 1986). It is likely that shiftworkers receive even less exposure to bright (day) light. Thus, a regimen of bright light exposure at critical times of day could provide an important entraining, and *re*entraining, influence in this population (Czeisler, et al., 1989; Eastman, 1987).

Pharmacological Interventions. -- There are a number of drugs that are effective in inducing sleep and in maintaining wakefulness. Few, however, can be recommended unequivocally to combat shift workers' sleep and alertness problems. Because sleep difficulties in shift work tend to be chronic, the use of sleeping pills is problematic. Futhermore, at least one study has concluded that improving daytime sleep with hypnotics does little to improve alertness or performance on the subsequent night shift (Walsh, et al., 1988). However, recent findings that a particular class of hypnotics, the short acting benzodiazapines, may be effective in circadian rhythms adjustment (Turek & Losee-Olson, 1986) introduces the possibility that acute use of such hypnotics may be beneficial in shift work applications (Turek & Van Reeth, 1988).

There is also evidence to suggest that other pharmacological agents may have applications in the shift work domain. Oral administration of tryptophan, for example, has been shown to be helpful in promoting sleep

onset (Hartmann & Spinweber, 1979; Hartmann, et al., 1976) without significantly impairing performance (Liebermann, et al., 1985). Similarly, melatonin has been shown to have short acting sedative-like properties (Anton-Tay, et al., 1971; Vollrath, et al., 1975) and it has been suggested that this drug may be particularly effective in treating sleep disturbance related to desynchronized circadian rhythms (Liebermann, et al., 1984).

With respect to maintaining alertness (as opposed to maintaining or inducing sleep), judicious use of caffeine would seem to be the most desirable approach. It has been shown, for example, that caffeine (equivalent to that found in about 3 cups of coffee) administered following restricted night sleep was effective in reducing daytime sleepiness. There is limited evidence, as well, that caffeine may enhance performance. However, as with any stimulant, the beneficial impact on waking function must be weighed against the negative effects on sleep and mood. Caffeine has been shown repeatedly to have detrimental effects on sleep and may cause anxiety, nervousness and gastrointestinal discomfort. Thus the timing of caffeine intake, relative to sleep placement, as well as the amount consumed must be carefully controlled.

In summary, there are a number of approaches that may be helpful in reducing the conflict between shift work and the human circadian timing system. Those discussed above comprise but a partial list of the possible strategies available. Regardless of the approach taken, however, it must be

kept in mind that the practice of shift work will forever be at odds with human circadian physiology. World economics and consumer demands notwithstanding, evolution has dictated that we are diurnal animals -- always have been, always will be. As such, the best we can expect from even the most effective intervention is that the conflict will be minimized.

References

Akerstedt, T. "Work Schedules and Sleep", Experientia 40:417-422, 1984.

Akerstedt, T. "Adjustment of Physiological Circadian Rhythms and the Sleep-Wake Cycle to Shiftwork", Hours of Work, S.Folkard, T. Monk (eds.) (New York, NY: John Wiley and Sons, 1985).

Akerstedt, T. "Sleepiness as a Consequence of Shift Work", Sleep 11(1):17-34, 1988.

Akerstedt, T. and Gillberg, M. "The Circadian Variation of Experimentally Displaced Sleep", Sleep 4(2):159-169, 1981.

Aschoff, J. "Die 24-Stunden Periodik der Maus Unter Konstanten Umgebungs Bedingungen", Naturwissenschaften 38:506-507, 1951.

Anton-Tay, F., Diaz, J.L. and Fernandez-Guardiola, G. "On the Effect of Melatonin Upon Human Brains: Its Possible Therapeutic Implications", Life Sciences 10:841-850, 1971.

Aschoff, J. "Circadian Rhythms in Man: A Self-Sustained Oscillator with an Inherent Frequency Underlies Human 24-Hour Periodicity", Science 148:1427-1432, 1965.

Aschoff, J. "Circadian Rhythms: Influences of Internal and External Factors on the Period Measured in Constant Conditions", Zeitschrift fuer Tierpsychologie 49:225-249, 1979.

Aschoff, J. (ed.), Handbook of Behavioral Neurobiology Vol. 4: Biological Rhythms (New York, NY: Plenum Press, 1981).

Aschoff, J. and Wever, R. "Spontanperiodik des Menschen bei Ausschluss aller Zeitgeber", Naturwissenschaften 49:337-342, 1962.

Aschoff, J. and Wever, R. "The Circadian System of Man", Handbook of Behavioral Neurobiology Vol. 4: Biological Rhythms, J. Aschoff (ed.) (New York, NY: Plenum Press, 1981).

Athanassenas, G. and Wolters, C.L. "Sleep After Transmeridian Flights", Night and Shift Work: Biological and Social Aspects Reinberg, A., Vieux, N. and Andlauer, P. (eds.),(Oxford: Pergamon Press, 1981).

Bjerner, B., Holm, A. and Swensson, A. "Diurnal Variation in Mental Performance: A Study of Three-Shift Workers", British J. of Industrial Medicine 12:103-110, 1955.

Blake, M.J.F. "Time of Day Effect on Performance in a Range of Tasks", Psychonomic Science 9:345-350, 1967.

Browne, R.C. "The Day and Night Performance of Teleprinter Switch Board Operators", Occupational Psychology 23, 121-126, 1949.

Buenning, E. "Opening address: Biological clocks", Cold Springs Harbor Symposia on Quantitative Biology, Biological Clocks (Baltimore, Maryland: Waverly Press, 1960).

Campbell, S. "Duration and Placement of Sleep in a 'Disentrained' Environment", Psychophysiology 21(1):106-113, 1984.

Campbell, S.S. and Zulley, J. "Ultradian Components of Human Sleep/Wake Patterns During Disentrainment", Ultradian Rhythms in Physiology and Behavior, H. Schulz and P. Lavie (eds.) (Berlin: Springer Verlag, 1985).

Campbell,S. and Zulley, J. "Napping as a Biological Rhythm: Disentrainment of the Human Sleep/Wake System", Sleep '86, W.P. Koella, F. Obal, H. Schulz, et al. (eds.) (New York, NY: Gustav Fischer Verlag, 1988).

Campbell, S., Kripke, D., Gillin, J., et al. "Exposure to Light in Healthy Elderly Subjects and Alzheimer's Patients", Physiology and Behavior 42:141-144, 1988.

Christie, M.J. and McBrearty, E.M.T. "Psychophysical Investigations of Post Lunch State in Male and Female Subjects", Ergonomics 22:307-323, 1979.

Colligan, M. and Tepas, D. "The Stress of Hours of Work", American Industrial Hygiene Association Journal 47(11):686-695, 1986.

Colquhoun, W.P. (ed.), Biological Rhythms and Human Performance (New York, NY: Academic Press, 1971).

Colquhoun, W.P. (ed.), Aspects of Human Efficiency: Diurnal Rhythms and Loss of Sleep (London: English Universities Press, 1972).

Colquhoun, P. "Rhythms in Performance", Handbook of Behavioral Neurobiology Vol. 4: Biological Rhythms, J. Aschoff (ed.) (New York, NY: Plenum Press, 1981).

Colquhoun, W., Blake, W. and Edwards, R. "Experimental Studies of Shiftwork II: Stabilized 8-Hour Shift Systems", Ergonomics 11:527-546, 1968.

Conroy, R.T. and Mills, J.N. (eds.) Human Circadian Rhythms (Baltimore, Maryland: Williams & Wilkins, 1970).

Czeisler, C., Moore-Ede, M. and Coleman, R. "Rotating Shift Work Schedules That Disrupt Sleep Are Improved by Applying Circadian Principles", Science 217:460-463, 1982.

Czeisler, C., Allan, J., Strogatz, S., et al. "Bright Light Resets the Human Circadian Pacemaker Independent of the Timing of the Sleep-Wake Cycle", Science 233:667-671, 1986.

Czeisler, C., Kronauer, R., Allan, J., et al. "Bright Light Induction of Strong (Type O) Resetting of the Human Circadian Pacemaker", Science 244:1328-1333, 1989.

De Candolle, A.P. Physiologie Vegetale Vol. 2 (Paris: Bechet Jeune, 1832).

De Mairan, J. "Observation botanique", Histoire de L'Academie Royale des Sciences 35-36, 1729.

Dement, W.C., Seidel, W.F., Cohen, S.A., et al. "Sleep and Wakefulness in Aircrew Before and After Transoceanic Flights", Aviation Space and Environmental Medicine 57(12):B14-28, 1986.

Dinges, D.F. "The Influence of the Human Circadian Timekeeping System on Sleep", Principles and Practice of Sleep Medicine, M.H. Kryger, T. Roth, W.C. Dement (eds.) (Philadelphia, PA.: W.B. Saunders Co., 1989.

Eastman, C. "Bright Light Improves the Entrainment of the Circadian Rhythm of Body Temperature to a 26-Hr Sleep-Wake Schedule in Humans", Sleep Research 15:271, 1986.

Eastman, C. "Bright Light in Work-Sleep Schedules for Shift Workers: Application of Circadian Rhythm Principles", Temporal Disorder in Human Oscillatory Systems, L. Rensing, U. an der Heiden and M. Mackey (eds.) (New York, NY: Springer-Verlag, 1987).

Folkhard, S., Knauth, P., Monk, T., et al. "The Effect of Memory Load on the Circadian Variation in Performance Efficiency Under a Rapidly Rotating Shift System", Ergonomics 19(4):479-488, 1976.

Folkard, S. and Monk, T.H. "Circadian Rhythms in Human Memory", British Journal of Psychology 71:295-307, 1980.

Folkard, S. and Monk, T.H. (eds.), Hours of Work: Temporal Factors in Work Scheduling (New York, NY: John Wiley & Sons, 1985).

Folkard, S., Monk, T.H. and Lobban, M.C. "Short and Long-Term Adjustment of Circadian Rhythms in "Permanent" Night Nurses", Ergonomics 21:785-799, 1978.

Folkhard, S., Marks, M., Minors, D., et al. "Circadian Rhythms in Human Performance and Affective State", Acta Psychiat. Belg. 85:568-581, 1985.

Foret, J. and Lantin, G. "The Sleep of Train Drivers: An Example of the Efects of Irregular Work Schedules on Sleep", Aspects of Human Efficiency: Diurnal Rhythms and Loss of Sleep, Colquhoun, W.P. (ed.), (London: English Universities Press, 1972).

Fuller, C.A., Lydic, R, Sulzman, F.M., et al. "Circadian Rhythm of Body Temperature Persists After Suprachiasmatic Lesions in the Squirrel Monkey", American Journal of Physiology 241:R385-R391,1981.

Graeber, R.C., Lauber, J.K., Connell, L.J., et al. "International Aircrew Sleep and Wakefulness After Multiple Time Zone Flights: A Cooperative Study", Aviation Space and Environmental Medicine 57(12):B3-9, 1986.

Halberg, F. "Physiologic 24-Hour Periodicity: General and Procedural Considerations with Reference to the Adrenal Cycle", Zeitschrift fuer Vitamin-, Mormon- und Fermentforschung 10:225-296, 1959.

Hartmann, E. and Spinweber, C.L. "Sleep Induced by L-tryptophan: Effects of Dosages Within the Normal Dietary Intake", Journal of Nervous and Mental Diseases 167:497-499, 1979.

Hartman, E., Spinweber, C.L., Ware, C. "L-tryptophan, L-lucine and placebo: Effects on Subjective Sleepiness", Sleep Research 5:57, 1976.

Hildebrandt, G., Rohmert, W. and Rutenfranz, J. "Twelve and 24 Hour Rhythms in Error Frequency of Locomotive Drivers and the Influence of Tiredness", International Journal of Chronobiology 2:97-110, 1974.

Inouye, S.T. and Kawamura, H. "Persistence of Circadian Rhythmicity in a Mammalian Hypothalamic "Island" Containing the Suprachiasmatic Nucleus", Proceedings of the National Academy of Sciences 76:5962-5966, 1979.

Kleitman, N. Sleep and Wakefulness (Chicago: University of Chicago Press, 1963).

Knauth, P., Rutenfranz, J., Herrmann, G., et al. "Re-entrainment of Body Temperture in Experimental Shift Work Studies", Ergonomics 21:775-783, 1978.

Laird, D.A. "Relative Performance of College Students as Conditioned by Time of Day and Day of Week", Journal of Experimental Psychology 8:50-63, 1925.

Lavie, P. "Ultradian Cycles in Wakefulness -- Possible Implications for Work-Rest Schedules", Hours of Work: Temporal Factors in Work Scheduling, Folkard, S. and Monk, T.H. (eds.), (New York, NY: John Wiley & Sons, 1985).

Lehman, M.N., Silver, R., Gladstone, W.R., et al. "Circadian Rhythmicity Restored by Neural Transplant. Immunocytochemical Characterization of the Graft and Its Integration with the Host Brain", Journal of Neuroscience 7(6):1626-1638, 1987.

Lewy, A., Kern, H.E., Rosenthal, N.E., et al. "Bright Artificial Light Treatment of a Manic-Depressive Patient with a Seasonal Mood Cycle", American Journal of Psychiatry, 139:1496-1498, 1982.

Lewy, A., Sack, R., Miller, L., et al. "Antidepressant and Circadian Phase-Shifting Effects of Light", Science 235:352-354, 1987.

Lieberman, H., Waldhauser, F., Garfield, G., et al. "Effects of Melatonin on Human Mood and Performance", Brain Research 323:201-207, 1984.

Lieberman, H.R., Corkin, S., Spring, B.J., et al. "The Effects of Dietary Neurotransmitter Precursors on Human Behavior", American Journal of Clincial Nutrition 42:366-370, 1985.

Mistlberger, R. and Rusak, B. "Mechanisms and Models of the Circadian Timekeeping System", Principles and Practice of Sleep Medicine, M.H. Kryger, T. Roth, W.C. Dement (eds.) (Philadelphia, PA.: W.B. Saunders Co., 1989.

Monk, T.H. "Circadian Rhythms in Subjective Activation, Mood, and Performance Efficiency", Principles and Practice of Sleep Medicine, M.H. Kryger, T. Roth, W.C. Dement (eds.) (Philadelphia, PA.: W.B. Saunders Co., 1989.

Monk, T.H. and Leng, V.C. "Time of Day Effects in Simple Repetitive Tasks", Acta Psychologia 51:207-221, 1982.

Moore, R.Y. and Eichler, V.B. "Loss of Circadian Adrenal Corticosterone Rhythm Following Suprachiasmatic Lesions in the Rat", Brain Research 42:201-206, 1972.

Moore, R.Y. and Lenn, N.J. "A Retinohypothalamic Projection in the Rat", Journal of Comparative Neurology 146:1-14, 1972.

Moore-Ede, M.C., Sulzman, F.M. and Fuller, C.A., The Clocks That Time Us (Cambridge, Massachusetts: Harvard University Press, 1982).

Prokop, O. and Prokop, L. "Ermudung und Einshlafen an Steuer", Zentralblatt fur Verkehrs-Medizin, VerkehrPsychologie und Angrenzende Gebiete 1:19-30, 1955.

Prosser, R.A. and Satinoff, E. "Suprachiasmatic Lesions Alter But Do Not Eliminate Circadian Body Temperature Rhythms in Rats", Federation Proceedings 43:906, 1984.

Reiter, R.J. "Neuroendocrinology of Melatonin", Melatonin: Clinical Perspectives, A. Miles, D. Philbrick, C. Thompson (eds.)(Oxford: Oxford University Press, 1988).

Reiter, R.J. "The Pineal Gland", DeGroot's Endocrinology, Vol. 1, Second Edition, L.J. Groot (ed.)(Philadelphia:Saunders, 1989).

Reppert, S.M., Weaver, D.R., Rivkees, S.A., et al. "Putative Melatonin Receptors in a Human Biological Clock", Science 242:78-81, 1988.

Richter, C.P. Biological Clocks in Medicine and Psychiatry (Springfield, Ill.: C.C. Thomas, 1965).

Richter, C.P. "Sleep and Activity: Their Relation to the 24-Hour Clock", Proceedings of the Association for Research on Nervous and Mental Disease 45:8-27, 1967.

Rosenthal, N.E., Sack, D.A., Carpenter, C.J., et al. "Antidepressant Effects of Light in Seasonal Affective Disorder", American Journal of Psychaitry 142:163-170, 1985.

Rusak, B. and Groos, G. "Suprachiasmatic Stimulation Phase Shifts Rodent Circadian Rhythms", Science 215:1407-1409, 1982.

Sasaki, M., Kurosaki, Y., Mori, A., et al. "Patterns of Sleep-Wakefulness Before and After Tranmeridian Flight in Commercial Airline Pilots", Aviation Space and Environmental Medicine 57(12):29-42, 1986.

Savides, T., Messin, S., Senger, C., et al. "Natural Light Exposure of Young Adults", Physiology and Behavior 38:571-574, 1986.

Stephan, F.K. and Zucker, I. "Circadian Rhythms in Drinking Behavior and Locomotor Activity of Rats are Eliminated by Hypothalamic Lesions", Proceedings of the National Academy of Sciences 69:1583-1586, 1972.

Terman, M. and Terman, J. "A Circadian Pacemaker for Visual Sensitivity?", Annals of the New York Academy of Sciences 453:147-161, 1985.

Turek, F. "Circadian Principles and Design of Rotating Shift Work Schedules", American Journal of Physiology 251:R636-638, 1986.

Turek, F. and Losee-Olsen, S. "A Benzodiazepine Used in the Treatment of Insomnia Phase-Shifts the Mammalian Circadian Clock", Nature 321: 167-168, 1986.

Turek, F.W. and Van Reeth, O. "Manipulation of the Circadian Clock with Benzodiazepines: Implications for Altering the Sleep-Wake Cycle", Pharmacopsychiatry 21:38-42, 1988.

Walsh, J., Sugerman, J., Muehlbach, M., et al. "Physiological Sleep Tendency on a Simulated Night Shift: Adaptation and Effects of Triazolam", Sleep 11(3):251-264, 1988.

Webb, W. and Agnew, H. "Effects of Rapidly Rotating Shifts on Sleep Patterns and Sleep Structure", Aviation, Space and Environmental Medicine 49(2):384-389, 1978.

Wegman, H.M. and Klein, K.E. "Jet-Lag and Aircrew Scheduling", Hours of Work, S.Folkard, T. Monk (eds.) (New York, NY: John Wiley and Sons, 1985).

Wegmann, H.M., Gundel, A., Naumann, M., et al. "Sleep, Sleepiness and Circadian Rhythmicity in Aircrews Operating on Transatlantic Routes", Aviation Space and Environmental Medicine 57(12):B53-64, 1986.

Weitzman, E.D. and Kripke, D.F. "Experimental 12-Hour Shift of the Sleep -Wake Cycle in Man: Effects on Sleep and Physiologic Rhythms", Biological Rhythms and Shift Work Johnson, L.C., Tepas, D.J., Colquhoun, W.P. and Colligan, M.J. (eds), (New York, NY: Spectrum Publications, 1982).

Wever, R.A., The Circadian System of Man (New York, NY: Springer Verlag, 1979).

Wever, R., Polasek, J. and Wildgruber, C. "Bright Light Affects Human Circadian Rhythms", Pfluegers Archives 396:85-87, 1983.

Winget, C.M., DeRoshia, C.W., Markley, C.L., et al. "A Review of Human Physiological and Performance Changes Associated with Desynchronosis of Biological Rhythms", Aviation Space and Environmental Medicine 55: 1085-1096, 1984.

Wojtczak-Jaroszowa, J. and Pawlowska-Skyba, K. "Night and Shift Work I: Circadian Variations in Work", Medycyna Pracy 18:1, 1967.

Zulley, J. and Campbell, S.S. "Napping Behavior During "Spontaneous Internal Desynchronization": Sleep Remains in Synchrony With Body Temperature", Human Neurobiology 4:123-126, 1985.

BIOLOGICAL RHYTHMS AND SHIFT WORK

APPENDIX TO

BIOLOGICAL RHYTHMS AND HUMAN PERFORMANCE

Scott S. Campbell

Institute for Circadian Physiology
Boston, Massachusetts

This contractor document was prepared for the OTA report entitled *Biological Rhythms and Shift Work*. It is being made available because it contains much useful information beyond that used in the OTA report. However, it is not endorsed by OTA, nor has it been reviewed by the Technology Assessment Board. References to it should cite the contractor, not OTA, as the author.

Submitted: October 17, 1989

BIOLOGICAL RHYTHMS AND HUMAN PERFORMANCE (APPENDIX)

As pointed out at the beginning of the accompanying review on Biological Rhythms and Human Performance, the natural light/dark cycle associated with the earth's rotation is the primary environmental synchronizer, or entrainer, for mammalian circadian rhythms. Indeed, it was the knowledge of this intimate relationship between the environment and physiology and behavior that led directly to the identification of the brain structures responsible for the generation and control of circadian rhythmicity (see Page 7 of the review). The neuronal systems involved in circadian control, and the influence of Zeitgebers on the timing of the circadian system, are discussed briefly in the review. The purposes of this Appendix are two-fold. First, the neural and endocrine components of the circadian "clock" are discussed in further detailed. Second, a more detailed explanation of the mechanisms of light transmission to the circadian system, and of the effects of light on mammalian circadian systems, is provided.

It should be emphasized that no attempt has been made here to provide an exhaustive review of these topics. Such a review is far beyond the scope of our commission, not to mention our expertise. Rather, a very general overview is presented here in an effort to provide more background to enable a better understanding of the mechanisms that regulate, both directly and indirectly, the timing of human performance.

Neural Control of Mammalian Circadian Rhythmicity

A putative circadian pacemaker must fulfill two primary requirements. First, it must be capable of independently generating a circadian rhythm; that is, it must be a self-sustaining oscillator. Second, the output of such a self-sustaining oscillator must be reflected in one or more overt rhythms (e.g., body core temperature). As mentioned in the body of the review, considerable experimental evidence indicates that the *suprachiasmatic nuclei (SCN)* satisfy both of these criteria. The following section reviews some of the findings that led to the identification of the SCN as the primary pacemaker of the mammalian circadian system.

Ablation of the SCN of rodents was one of the first techniques employed to examine the role of these neural structures in circadian regulation (e.g., Rusak & Zucker, 1979). Ablation of the SCN led to the loss of circadian rhythmicity in a large number of overt rhythms at the endocrine, behavioral and physiological levels. Moreover, destruction of the SCN resulted in disruption of photic entrainment of these functions. Such studies clearly supported the hypothesis that the SCN serves as the central pacemaker of the mammalian circadian system.

However, the results of these lesion studies were not conclusive, for several reasons. First, the observed loss of rhythmicity may have resulted from damage to other systems, rather than the SCN specifically. Second, effects of lesions may be situation-specific: rhythmic function surviving the

ablation may be detected only under limited conditions. Finally, rhythmicity may survive ablation of the SCN, but only at a level undetectable by the statistical procedure employed. In order to establish more firmly the properties and functional role of the SCN, additional studies employing alternative procedures were required.

The finding that metabolic activity in SCN neurons exhibited a daily rhythm (Schwartz, et al., 1980) indicated clearly that the SCN met the first requirement of a pacemaker -- that it acted as a self-sustaining oscillator. These studies showed that neuronal activity in the SCN was highest during the subjective day and declined dramatically during subjective night. The self-sustaining nature of this oscillation was further confirmed by the finding that such rhythms persisted in an SCN "island", formed by a knife cut around the SCN (Inouye & Kawamura, 1979). This result clearly demonstrated that SCN rhythmicity did not require neural input from outside the hypothalamus. Perhaps even more convincing evidence of the intrinsic nature of SCN rhythmicity came from studies of neural activity in hypothalamic tissue maintained *in vitro* (e.g., Meijer & Rietveld, 1989). Slice preparations from rats and hamsters have been reported to show persistent circadian rhythmicity.

With regard to the second requirement of a pacemaker -- that its output be reflected in overt rhythms -- several procedures have been employed. The SCN "island" preparation described above demonstrated that while

rhythmicity was maintained within the SCN, it was abolished outside the island. Other manipulations of the intact SCN have been shown to affect overt rhythms, as well. For example, electrical stimulation in the SCN was shown to produce phase-dependent shifts of activity rhythms in hamsters and feeding rhythms in rats (Rusak & Groos, 1982). The most dramatic evidence that the SCN functions as a circadian pacemaker comes from studies showing the restoration of circadian rhythmicity in SCN-lesioned rats and hamsters when fetal hypothalamic tissue containing the SCN is transplanted to the brains of the lesioned animals (Sawaki, et al., 1984; Lehman, et al., 1987). Such implants convey the period of the donor's SCN rhythm, providing further evidence that the SCN is a pacemaker, rather than a passive mechanism allowing expression of an unobserved rhythm within the host animal.

What is it within the SCN that enables this neuronal group to act as a pacemaker? What is the mechanism of this biological clock? At present, there are no adequate answers. The SCN constitutes a complex system, with tens of thousand of neurons of various types, mediated by a wide variety of neurotransmitters, neuropeptides and synaptic relations. While major efferent pathways have been identified, the roles of the cells involved remains unclear. What is clear, however, is that photic stimulation has an enormous influence on the mammalian circadian system. The mechanisms of photic entrainment are the topic of the next section.

Entrainment by Light

For most animals, it is adaptive to restrict activity periods to times of the day when optimal environmental conditions prevail, and to cease activity during non-optimal intervals. While the endogenous circadian timing system provides a mechanism for the general timing of behaviors, the system (which typically is not equal to 24 hrs) must continually be adjusted to compensate for the difference between the inherent circadian period and the 24-hour day. Simply, external time cues must synchronize the endogenous rhythm to exactly 24 hours. It is no surprise that most organisms have evolved mechanisms to take advantage of light as an entraining agent, or Zeitgeber.

The process by which entrainment occurs has been studied by examining the effects of discrete light pulses on the circadian rhythms of animals living in constant darkness. Such light pulses cause phase shifts of the free-running rhythms, the extent and direction of the shifts being dependent on the phase at which the pulse is given. The results of a number of such pulses may be plotted to obtain a *phase response curve (PRC)* for light, as illustrated in Figure 1 (next page). Note that phase may be advanced or delayed as a function of the phase at which the light pulse is delivered. In addition, there is a substantial "dead zone" during which no phase shifts are observed. Only recently have researchers attempted to obtain a PRC to light for the human circadian system. The methodology employed in non-human PRC studies is virtually impossible to use in humans. However, using different approaches,

several groups have described similar curves (Czeisler, et al., 1989; Dawson, et al., 1989; Homna, et al., 1987).

Natural light entrains circadian rhythms because their inherent periods are close to 24 hrs. However, artificial light can entrain circadian rhythms only if the difference between endogenous and imposed periods does not exceed a critical interval, which is equivalent to the maximum phase shift obtained with the light source under identical conditions. For example, if the maximum shift obtained by a light pulse is 6 hours, then a circadian rhythm with a free-running period of 25 hrs may be entrained by that pulse to periods within a range of roughly 19 to 31 hours. This range is referred to as the Zeitgeber's "limits of entrainment". In practice, limits of entrainment are quite flexible and depend on factors such as the species studied and the rapidity with which the entrainment procedure is undertaken.

Pathways of Photic Entrainment

As might be expected, photic entrainment in mammals is mediated through photoreceptors in the retina. Congenitally blind mammals cannot be entrained to light/dark cycles. (This is not the case in birds and lizards, however, where pineal and encephalic photoreceptors enable photic entrainment). Retinal photic information is transmitted directly to the SCN via the retinohypothalamic tract (RHT). The SCN also receives photic information through the geniculohypothalamic tract (GHT), which originates from retinorecipient neurons in the lateral geniculate nucleus. Both tracts

appear to play a role in entrainment, though their precise functional roles remain uncertain. The RHT is sufficient to mediate entrainment following LGN ablation in rats, though phase-advancing effects of photic stimulation are attenuated in this preparation (Harrington & Rusak, 1986). Electrical stimulation of the GHT, on the other hand, produces phase shifts similar to those produced by photic stimulation.

The pathways by which entrainment information is transmitted from the SCN to other oscillators and physiological, endocrine and behavioral processes remains unclear. The fact that the SCN "island" preparation eliminates most circadian rhythmicity outside the island indicates that the timing information from the SCN is carried by neural efferent pathways. Such projections are extensive, with most terminating within the hypothalamus. However, little is known about how these projections interact with other neural mechanisms to generate, synchronize and entrain the overt rhythms that characterize the circadian timing system.

Nonphotic Entrainment

While the natural alternation between light and dark provides the most important entraining cue for the mammalian circadian system, it certainly does not provide the only one. Other factors that have been shown to effectively entrain circadian rhythms include food, ambient temperature and, especially in humans, social cues.

Among these non-photic entrainers, food availability has been most

carefully examined. It has been shown, for example, that rats provided with food for a fixed interval each day exhibit increased motor activity, as well as physiological changes, in anticipation of the mealtime (Boulos & Terman, 1980). Such entrainment is rapid (i.e., within a few days) and is generated independently of lighting schedules. Thus, if a light/dark cycle is replaced by constant light, the animal's rest/activity cycle will free-run. Yet, it's pre-meal activity will continue to be entrained by the food schedule. As with photic stimulation, food availability is subject to limits of entrainment. Since circadian rhythms in anticipatory feeding activity survive SCN lesions, it appears that neural mechanisms in other hypothalamic areas may act as separate oscillators to control this behavior (Mistlberger & Rechtschaffen, 1984).

Ambient temperature is a potent entrainer of circadian cycles in poikilothermic species, but less so in homeothermic animals. In the latter group, the mechanism of entrainment by temperature is unclear. It is unlikely to involve a direct temperature effect on neural structures, however, since brain temperature is homeostatically controlled. It has been suggested that the effect on circadian rhythms may be indirect, through an influence of temperature on the sleep/wake cycle. Altered timing of sleep and waking would, in turn, change meal timing and exposure to environmental light, thereby entraining the circadian system (Mistlberger & Rusak, 1989).

Although humans circadian rhythms are probably most affected by social

cues, other species, such as sparrows, rats and beavers have also been shown to be influenced by social interaction. As with ambient temperature, the mechanism by which social cues entrain circadian rhythms is unknown. Although potentially strong, it is clear that the entaining effects of social cues are not universal. For example, rats and hamsters exposed to visual, auditory and olfactory contact of conspecifics, but housed individually, may not become synchronized. Moreover, several cases have been reported of blind humans living in society, yet exhibiting free-running rhythms (e.g., Miles, et al., 1977).

Hormonal Influences

Increasing evidence suggests that hormones also may play an important, though apparently not essential, regulatory role in circadian rhythmicity, perhaps by modulating coupling relationships between oscillators and between oscillators and overt rhythms. Gender-specific hormonal secretion (e.g., estradiol, testosterone) has been shown to influence daily and seasonal activity rhythms in rats and hamsters. In addition, circadian effects of melatonin, a hormone synthesized by the pineal and the retina, have been reported in a number of species.

The pineal gland of mammals is functionally related to the visual system and the circadian production of melatonin is entrained by the environmental photoperiod to which an animal is exposed (Reiter, 1981). Specifically, light suppresses pineal melatonin synthesis during the day, while during the dark

period, synthesis and secretion of melatonin is at a daily maximum. Photoperiodic information is received by the pineal via indirect neuronal connections with the SCN. Although the functional roles of the pineal and melatonin in non-human mammals have been described, their roles in the circadian physiology of humans remains unclear. However, it has been shown that timed exposure to bright light can shift the phase of melatonin secretion (e.g., Sack & Lewy, 1988). In addition, oral administration of melatonin has been reported to enhance nighttime sleepiness (Arendt, et al., 1984), increase sleep duration in chronic insomniacs (MacFarlane, et al., 1989) and alleviate jet-lag after transmeridian flights (Arendt, et al., 1986).

Such findings emphasize the intimate relationship between the pineal/melatonin system and the circadian/sleep-wake systems. Although that relationship is not yet well-defined, a feedback mechanism between the pineal and the SCN has been suggested, whereby melatonin secretion may act to synchronize the circadian pacemaker, specifically with regard to locomotor activity (Chesworth, et al., 1987). The notion of a feedback relationship between SCN and the pineal is supported by the recent reports of melatonin receptors in the SCN of rodents (Reppert, et al., 1988; Vanecek, et al., 1987).

Functions of the Pacemaker

It is tempting to view the circadian system as being controlled entirely by a pacemaker located within the discrete boundaries defined by the

suprachiasmatic nuclei. Predictably though, a system that is so prominent throughout physiology and behavior and apparently so critical to the overall well-being of the organism, cannot be delineated that easily. While all primary "roads" carrying circadian information appear to lead to the SCN, there is growing evidence that the traffic patterns are not simple and that byways may exist. As mentioned previously, meal-related anticipatory activity appears to survive SCN ablation. Likewise, some researchers have reported persisting circadian temperature rhythms in rats and in squirrel monkeys with SCN lesions (Prosser & Satinoff, 1984; Fuller, et al., 1981).

The multiple oscillator hypothesis of human circadian regulation (see, for example, Wever, 1979) is based on the finding that about 30% of all subjects studied under time free conditions exhibited a phenomenon referred to as "spontaneous internal desynchronization", in which the rest/activity and temperature rhythms display different periods. Although interpretation of these data has been challenged (Zulley & Campbell, 1985) and mathematical models assuming a single pacemaker can account for internal desynchronization (e.g., Eastman, 1982), such data may be viewed as supporting the hypothesis that more than one oscillator is required for regulation of circadian systems.

Taken together, the evidence from both human and non-human studies suggests that circadian regulation in mammals is governed by a hierarchical system of oscillators. The SCN are probably the locus of a dominant

pacemaker that, under normal circumstances, controls the timing of numerous subordinate oscillators located outside the SCN, and in some cases outside the brain. These oscillators, in turn, may control the expression of overt rhythms. The subordinate oscillators may also exert some influence on the SCN given the proper circumstances (Stephan, 1986). In the absence SCN control, secondary oscillators may drive overt processes independently, resulting in desynchronized rhythms.

Little is known about the interaction between the dominant circadian pacemaker and the hypothesized secondary oscillators. Clarification of these relationships will require a great deal more work, as will identification of the functional roles of the various components of the circadian system. These issues, combined with the continued examination of the variables that influence circadian timing, represent challenging, yet essential steps toward a complete understanding of biological rhythms.

References

The author borrowed heavily and often from three reviews of the literature in the preparation of this Appendix. For those interested in obtaining a more detailed understanding of the subject matter presented here, a reading of the original reviews is highly recommended:

Hasting, J.W., Rusak, B. and Boulos, Z. "Circadian Rhythms: The Physiology of Biological Timing", Comparative Physiology, 4th Edition, C.L. Prosser (ed.) (New York, NY: Wiley, 1989, in press).

Mistlberger, R. and Rusak, B. "Mechanisms and Models of the Circadian Timekeeping System", Principles and Practice of Sleep Medicine, M.H. Kryger, T. Roth, W.C. Dement (eds.) (Philadelphia, PA.: W.B. Saunders Co., 1989.

Rusak, B. "The Mammalian Circadian System: Models and Physiology", J. Biological Rhythms 4(2):121-134, 1989.

Other references cited in the text:

Arendt, J., Borbely, A., Franey, C., et al. "The Effect of Chronic Small Doses of Melatonin Given in the Late Afternoon on Fatigue in Man: A Preliminary Study", Neurosci. Let. 45(3):317-321, 1984.

Arendt, J., Aldhous, M. and Marks, J. "Alleviation of Jet Lag by Melatonin: Preliminary Results of Controlled Double Blind Trial", Brit. Med. J. 292:1170, 1986.

Boulos, Z. and Terman, M. "Food Availability and Daily Biological Rhythms", Neurosci Biobehav Rev 4:119-131, 1980.

Chesworth, M., Cassone, V. and Armstrong, S. "Effects of Daily Melatonin Injections on Activity Rhythms of Rats in Constant Light", Am J Physiol 253(1):R101-107, 1987.

Czeisler, C., Kronauer, R., Allan, J., et al. "Bright Light Induction of Strong (Type O) Resetting of the Human Circadian Pacemaker", Science 244:1328-1333, 1989.

Dawson, D., Morris, M. and Lack, L. "Average Phase Response Curve in Humans for a 4hr Exposure to Evening Light", Sleep Res. 18:413, 1989.

Fuller, C., Lydic, R., Sulzman, F, et al. "Circadian Rhythm of Body Temperature Persists After Suprachiasmatic Lesions in the Squirrel Monkey", Am J Physiol 241:R385-391, 1981.

Harrington, M. and Rusak, B. "Lesions of the Thalamic Intergeniculate Leaflet Alter Hamster Circadian Rhythms", J. Biol. Rhythms 1:309-325, 1986.

Homna, K., Homna, S. and Wada, T. "Entrainment of Human Circadian Rhythms by Artificial Bright Light Cycles", Experientia 43:572-574, 1987.

Inouye, S.T. and Kawamura, H. "Persistence of Circadian Rhythmicity in a Mammalian Hypothalamic "Island" Containing the Suprachiasmatic Nucleus", Proceedings of the National Academy of Sciences 76:5962-5966, 1979.

Lehman, M., Silver, R., Gladstone, W., et al. "Circadian Rhythmicity Restored by Neural Transplant: Immunocytochemical Characterization of the Graft and Its Integration with the Host Brain", J. Neurosci. 7:1626-1638, 1987.

MacFarlane, J., Cleghorn, J.and Brown, G. "Soporific Effects of Exogenous Melatonin in Patients with Chronic Insomnia", Sleep Research 18:60, 1989.

Meijer, J. and Rietveld, W. "Neurophysiology of the SCN in Rodents", Physiol. Rev. 1989 (in press).

Miles, L., Raynal, D. and Wilson, M. "Blind Man Living in Normal Society has Circadian Rhythms of 24.9 Hours", Science 198:421-423, 1977.

Mistlberger, R. and Rechschaffen, A. "Recovery of Anticipatory Activity to Restricted Feeding in Rats with Ventromedial Hypothalamic Lesions", Physiol Behav 33:227-235, 1984.

Prosser, R. and Satinoff, E. "Suprachiasmatic Lesions Alter But Do Not Eliminate Circadian Body Temperature Rhythms in Rats", Fed Proc 43:906, 1984.

Reiter, R. "The Mammalian Pineal Gland: Structure and Function", Am. J. Anat. 162:287-313, 1981.

Reppert, S.M., Weaver, D.R., Rivkees, S.A., et al. "Putative Melatonin Receptors in a Human Biological Clock", Science 242:78-81, 1988.

Rusak, B. and Groos, G. "Suprachiasmatic Stimulation Phase Shifts Rodent Circadian Rhythms", Science 215:1407-1409, 1982.

Rusak, B. and Zucker, I. "Neural Regulation of Circadian Rhythms", Physiol. Rev. 59:449-526, 1979.

Sawaki, Y., Nihonmatsu, I. and Kawamura, H. "Transplantation of the Neonatal Suprachiasmatic Nuclei into Rats with Complete Bilateral Suprachiasmatic Lesions", Neuroscience Research 1:67-72, 1984.

Schwartz, W., Davidsen, L. and Smith, C. "Deoxyglucose uptake rhythms in rat suprachiasmatic nucleus neurons", J. Comp. Neurol. 189:157-167, 1980.

Vanecek, J., Pavlik, A. and Illnerova, H. "Melatonin Receptors in Hypothalamus", Brain Res 435:359-362, 1987.

Wever, R.A., The Circadian System of Man (New York, NY: Springer Verlag, 1979).

Zulley, J. and Campbell, S.S. "Napping Behavior During "Spontaneous Internal Desynchronization": Sleep Remains in Synchrony With Body Temperature", Human Neurobiology 4:123-126, 1985.

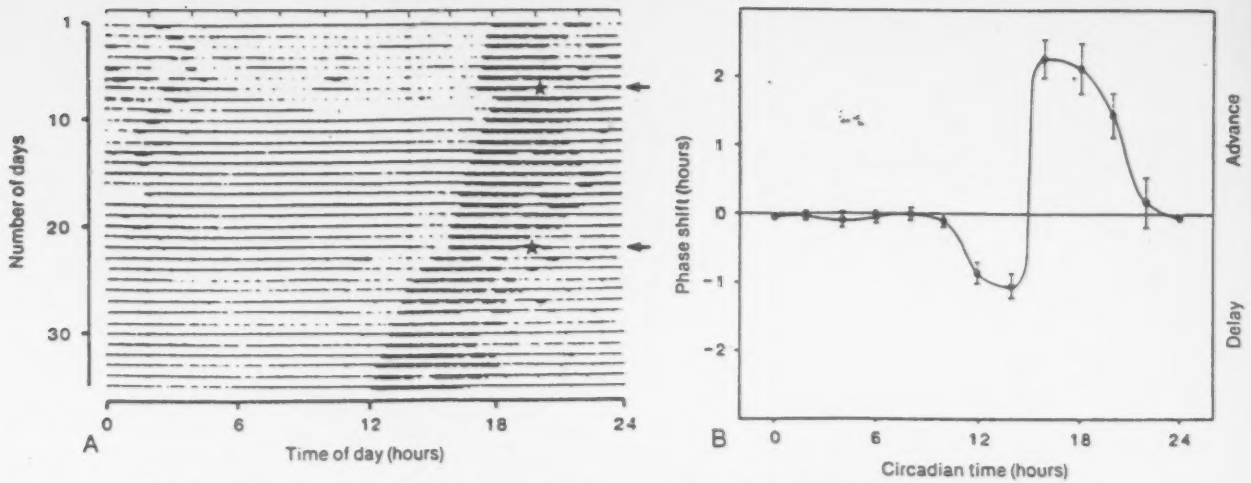

Figure 11–2. *A*. Event record of hamster wheel-running activity in constant darkness (DD). Each line represents 24 h, with time reading left to right and successive days aligned top to bottom. Each revolution of the running wheel causes a single vertical deflection of the event record pen. A solid dark line is thus formed during continuous running. In this chart, the onset of continuous running begins earlier each day, i.e., τ of the free-running rhythm is less than 24 h. A 15-min light pulse (marked by a star on the day indicated by the first arrow), presented several hours after the beginning of the daily running phase, causes the rhythm to shift to a later time on subsequent days. This type of shift is termed a "delay" shift. The second light pulse, indicated by the other arrow, was presented near the end of the daily running phase. It also produced a phase shift, but in the opposite direction, so that activity began and ended earlier on subsequent days. This is an "advance" phase shift.

B. The phase response curve for hamsters summarizes the relationship between the time at which a light pulse is presented and the direction of the phase shift produced. To construct this curve, the period of the circadian rhythm, usually different from 24 h, is first normalized to a 24-h time scale, referred to on the abscissa as circadian time (CT). For nocturnal rodents, CT12 is, by convention, the time when daily running activity begins. When a light pulse is presented around CT12, a delay phase shift of about 1 h occurs on average. This is indicated on the ordinate by a −1. The largest delay shifts occur at about CT13–14. The largest advance shifts (positive sign) occur at about CT16–18. No significant phase shift occurs when light pulses are presented from CT0 to CT10, which is the hamster's daily rest phase. In functional terms, a light pulse that occurs early in the active phase of a nocturnal (night-active) rodent is perceived as a late sunset. If the rodent is exposed to light at this time, it must mean that it has left its burrow too early and that the circadian clock is operating too fast. The clock thus immediately compensates by delay shifting (or slowing down briefly), so that the next day the rodent awakens a bit later. Similarly, a light pulse occurring near the end of the active phase simulates an early sunrise. The clock briefly accelerates to advance the activity rhythm so that the next day the hamster will begin and end its activity earlier and thus avoid being caught out of its burrow when the sun has risen. Since the intrinsic period of circadian rhythms is usually slightly different from 24 h and since the day-night cycle is exactly 24 h, these small clock adjustments must be made at least every few days if the organism is to remain in synchrony with its environment. (Reprinted with permission from Takahashi JS, Zatz M: Regulation of circadian rhythmicity. Science 217:1104–1111, 1982.)

Copied from Mistlberger & Rusak, 1989